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Synthesis of Heterocycles. Construction of the 1-Azabicyclo[2.2.1]heptyl System by Sequential Ring-Closure of Acyclic β-Ammonio Substituted Radicals

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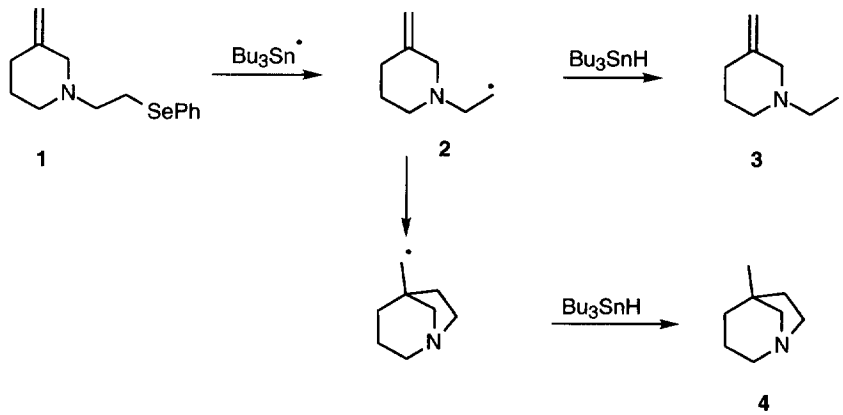
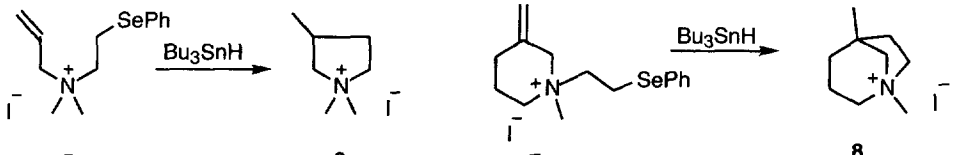
Abstract: Treatment of an irradiated solution of 1-methyl-1-(2-propynyl)-1-bis(2-phenylselenylethyl)ammonium iodide in *tert*-amyl alcohol with tributyltin hydride is found to be an effective procedure for the synthesis of 1,4-dimethyl-1-azoniabicyclo-[2.2.1]heptane iodide. Attachment of a trimethylsilyl or phenyl substituent to the terminal carbon of the triple bond in the alkynyl salt leads to bridgehead-substituted bicyclic heterocyclic salts. Copyright © 1996 Elsevier Science Ltd

During a recent study[1] directed to the synthesis of heterocyclic bicycloalkanes with nitrogen at the bridgehead we observed that reaction of the amine **1** with tributyltin hydride gave reduced material **3** as the predominant product rather than the target molecule, 1-aza-5-methylbicyclo[3.2.1]octane (**4**); the latter was formed as a minor constituent only (ratio of **3**:**4** = 9:1). This came as something of a surprise because by analogy with the behaviour of its carbocyclic analogue, the 3-methylenecyclohexylethyl radical, which undergoes facile ring-closure, the species **2** was expected to rearrange readily and give largely the bicyclic amine **4**.

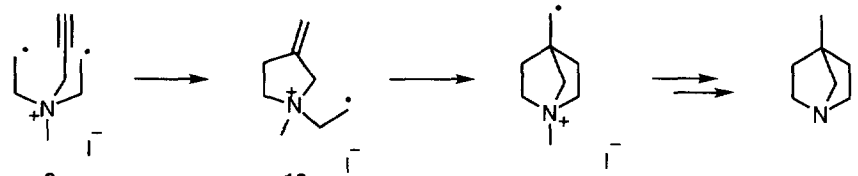


We suspected[1] that the extent of cyclisation could be improved if the derived quaternary ammonium salt were used as precursor instead of the free amine **1**. Since this type of substrate had not been used previously in radical cyclisations[2], we undertook a preliminary study of a model system, allyldimethyl-2-phenylselenylethylammonium iodide **5**. It was found that treatment of **5** in *tert*-amyl alcohol at 80°C with Bu_3SnH gives excellent yields of the hetereocyclic compound **6**. If required subsequently, the parent amine could be generated by demethylation of the quaternary salt by reaction with strong nucleophiles (eg DABCO®/DMF[3]). Application of this methodology to the corresponding salt **7**, derived from reaction of the amine **1** with iodomethane, also proved to be successful. Thus, treatment of a solution of **7** in *tert*-amyl alcohol at 105°C with Bu_3SnH added over 15 minutes afforded 1,5-dimethyl-1-azoniabicyclo[3.2.1]octane iodide (**8**) exclusively and in high yield (87%).



5 **6** **7** **8**

One of our primary objectives was to exploit these ammonium salts for the development of a viable synthesis of related heterocycles and, in particular, the 1-azabicyclo[2.2.1]heptyl system **12** some of the derivatives of which have been to shown to possess important physiological properties[4]. However, where the piperidinium salt **7** could be prepared in a relatively short sequence from commercially-available 3-(hydroxymethyl)piperidine, we were unable to devise an economical procedure leading to its five-membered analogue, the precursor to radical **10**. To circumvent this problem, we were strongly attracted to an alternative strategy commencing with an open-chain precursor which, in principle, would deliver the target molecule via a sequential set of radical ring-closure reactions. The type of process envisaged is illustrated in the route depicted below. By way of explanation, the radical centres in diradical **9** would be expected to be generated in a stepwise manner and, accordingly, **9** is regarded as an imaginary species and would not function as an intermediate in the reaction.

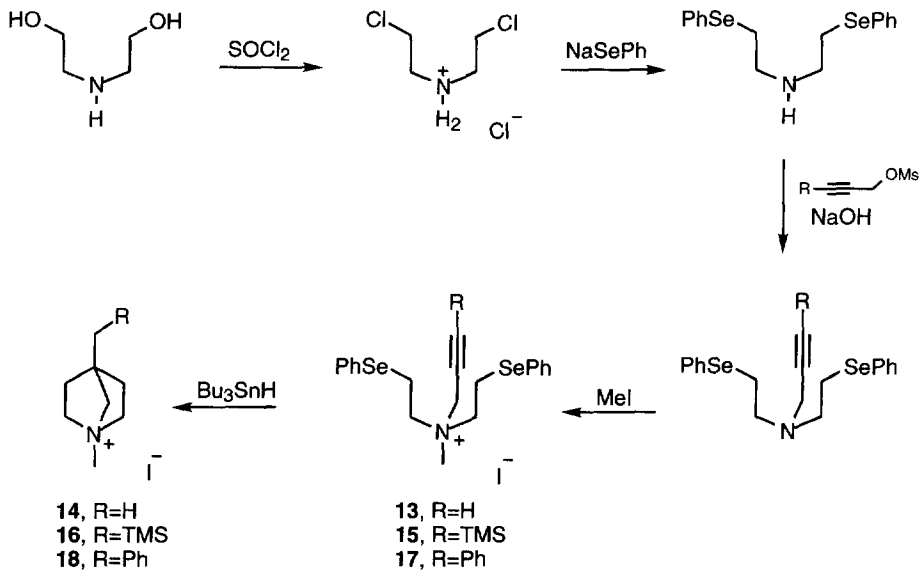


9 **10** **11** **12**

The diselenide **13** was chosen as an appropriate starting material for the transformation; its synthesis from diethanolamine was accomplished (54% yield) via the four-step sequence depicted in Scheme 1. In practice, a solution of the ammonium salt **13** in *tert*-amyl alcohol was held at 100°C and

irradiated with a 300W tungsten lamp whilst being treated dropwise over 15 minutes with a solution of tributyltin hydride (2.2 equivalents) in *tert*-amyl alcohol (0.025M). After a further 30 minutes, the reaction mixture was cooled and the solvent evaporated. Trituration of the residue with ether gave a fine white solid which by ^{1}H and ^{13}C NMR spectroscopic analysis was identified as the bicyclic salt, 1,4-dimethyi-1-azoniabicyclo[2.2.1]heptane iodide (**14**). A simple recrystallisation from C_6H_6/CH_2Cl_2 gave **14** in excellent yield (79%; 42% overall from diethanolamine). Signals that could be ascribed to either acyclic or monocyclic products corresponding to the interception of the radical intermediates shown above were not detected.

Scheme 1



14, R=H
16, R=TMS
18, R=Ph

13, R=H
15, R=TMS
17, R=Ph

The high yield of bicyclic product combined with the fact that it was produced without contamination is most impressive and exceeded our most optimistic expectations, because we had anticipated that at least some of each of the intermediate radicals would have been trapped by the Bu_3SnH.

Use of 3-mesyl-1-trimethylsilylpropyne and 3-mesyl-1-phenylpropyne as alternative alkylating agents in Scheme 1 afforded the corresponding diselenides **15** and **17**, respectively, in good yield. When each of these was exposed to Bu_3SnH under the same conditions employed for reduction of **13**, the corresponding 1-azoniabicyclo[2.2.1]heptane salts **16** and **18** were obtained in very high yields (see Table below). These derivatives contain rather more versatile substituents at the carbon bridgehead position than **13** and demonstrate the wider scope of the procedure.

Substrate[5]	Product[5]	Yield, %
13	**14**	79 (42[a])
15	**16**	87 (45[a])
17	**18**	91 (46[a])

[a] Overall yield from diethanolamine

In summary, this approach represents a very attractive entry into the 1-azabicyclo[2.2.1]heptyl system. We are currently planning to exploit the facility for ring-closure exhibited by these acyclic ammonium salts for the synthesis of derivatives of **12** which are known to be physiologically active as well as for other bicycloalkanes with nitrogen at the bridgehead.

Acknowledgements We thank the Australian Research Council for financial support of this work.

References and Notes

1. Della, E. W.; Knill, A. M. *J. Org. Chem.* submitted for publication.

2. As far as we are aware the only related positively-charged nitrogen-containing radicals that have been employed in radical cyclisations are the aminium cation radicals described by Newcomb and Deeb (see, eg, Newcomb, M.; Deeb, T. M. *J. Am. Chem. Soc.*, **1987**, *109*, 3163-3164); interestingly, although these nitrogen-centred radicals are significantly different from those involved in this work, they yield β-ammonio substituted radicals upon cyclisation.

3. Ho, T. L. *Synthesis*, **1972**, 702-703.

4. For leading references see Boelsterli, J.; Eggnauer, U.; Pombo-Villar, E.; Weber, H.-P.; Walkinshaw, M.; Gould, R. O. *Helv. Chim. Acta*, **1992**, *75*, 507-512, refs 2(a)-2(k). Cottrell, I. F.; Hands, D.; Kennedy, D. J.; Paul, K. J.; Wright, S. H. B.; Hoogsteen, K. *J. Chem. Soc. Perkin Trans I*, **1991**, 1091-1097, refs 1-3.

5. All these new compounds gave satisfactory microanalytical combustion data and their ^{1}H and ^{13}C NMR spectra were in accord with the designated structures.

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